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Background

The objective of the present analysis was to systematically examine the effect of intracoronary bone marrow cell (BMC) therapy on left ventricular function after ST-segment elevation myocardial infarction in various subgroups of patients by performing a collaborative meta-analysis of randomized controlled trials.

Methods

We identified all randomized controlled trials comparing intracoronary BMC infusion as treatment for ST-segment elevation myocardial infarction . We contacted the principal investigator for each participating trial to provide summary data with regard to different prespecified subgroups (age, diabetes mellitus, time from symptoms to percutaneous coronary intervention, infarct related artery, left ventricular (LV) end-diastolic volume index (EDVI), LV ejection fraction (EF), infarct size, presence of microvascular obstruction, timing of cell infusion, and injected cell number) and 3 different endpoints (change in LVEF, LVEDVI and LV end-systolic volume index (ESVI)).

Results

Data from 16 studies were combined including 1641 patients (984 cell therapy, 657 controls). The absolute improvement in LVEF was greater among BMC treated patients compared to controls: (2.55% increase, 95% Confidence Interval (CI) 1.83 to 3.26, $p<0.001$). Cell therapy significantly reduced LVEDVI and LVESVI (-3.17 mL/m², 95% CI -4.86 to -1.47, $p<0.001$; -2.60 mL/m², 95% CI 3.84 to -1.35, $p<0.001$, respectively). Treatment benefit in terms of LVEF improvement was more pronounced in younger patients (age <55, 3.38%, 95% CI 2.36 to 4.39) compared to older patients (age ≥55 years, 1.77%, 95% CI 0.80 to 2.74, $p=0.03$). This heterogeneity in treatment effect was also observed with respect to the reduction in LVEDVI and LVESVI. Moreover, patients with baseline LVEF<40% derived more benefit from intracoronary BMC therapy. LVEF improvement was 5.30%,

95% CI 4.27 to 6.33 in patients with LVEF <40% compared to 1.45%, 95% CI 0.60 to 2.31 in LVEF ≥40%, p<0.001. No clear interaction was observed between other subgroups and outcomes.

Conclusion

Intracoronary BMC infusion is associated with improvement of LV function and remodeling in patients after ST-segment elevation myocardial infarction . Younger patients and patients with a more severely depressed LVEF at baseline derived most benefit from this adjunctive therapy.

Key words Cell therapy, ST-segment elevation myocardial infarction , ventricular function, meta-analysis

Introduction

Previous meta-analyses of randomized trials have shown that intracoronary bone marrow cell (BMC) infusion in ST-segment elevation myocardial infarction (STEMI) patients has moderate positive results on the recovery of left ventricular (LV) function.(1, 2) Based on more detailed analyses from the individual trials, certain subgroups seem to have more benefit.

In some studies, patients with long delay from onset symptoms to revascularization, larger myocardial infarction (anterior myocardial infarction) and reduced baseline LV ejection fraction (EF) were more likely to benefit from BMC therapy.(3-5) Regarding microvascular obstruction (MVO), the subgroup effect remains unclear since 2 studies reported different outcomes of BMC therapy in this patients group.(6, 7) Furthermore, aging and risk factors for coronary artery disease affect the functional activity of endogenous stem and progenitor cells in experimental models, thereby potentially limiting the therapeutic potential of these cells.(8)

However, the individual trials have not been large enough to explore outcomes reliably within such subgroups. Identifying the characteristics of the patients who will ultimately benefit from cell therapy is essential to allow for efficient translation of this novel therapy to clinical practice. Therefore, the aim of this collaboration was to assess the effects of intracoronary BMC on LVEF, LV end-diastolic volume index (EDVI) and LV end-systolic volume index (ESVI) in various subgroups of STEMI patients based on pooled patient data.

Methods

Data sources and study selection

We performed a computerized literature search from 1980 to February 2013 of the Pubmed, Embase, Cochrane database, the Current Controlled Trials Register and KoreaMed, IndMed and LILACS by using search terms that included "bone marrow cells, "stem cell", "precursor cell", "progenitor cell", "myocardial ischemia", "myocardial infarction," "ischemic heart disease", "coronary heart disease", and "heart failure" (see Appendix1). Only English language publications were selected. Additionally, we manually searched the conference abstracts of the American Heart Association, American College of Cardiology, European Society of Cardiology and Transcatheter Cardiovascular Therapeutics to identify additional unpublished studies. Finally, the bibliographies of identified studies and relevant review articles were screened for potentially suitable studies.

We included a study if: 1) it was a randomized, controlled trial; 2) patients were included with a clinical diagnosis of STEMI, treated with percutaneous coronary intervention (PCI); 3) a single intracoronary infusion of autologous BMC (irrespective of the type and number of isolated cells) within one month after STEMI was compared to a control arm not receiving BMC (e.g. infusion of control media or standard treatment). Studies were excluded if: 1) there were less than 30 participants in the cell therapy arm; 2) follow-up was less than 3 months; 3) BMCs were cultured in vitro for longer than 1 day prior to intracoronary infusion, or 4) granulocyte colony-stimulating factor (G-CSF) or macrophage colony-stimulating factor (M-CSF) were administrated as co-intervention.

Study identification was done by two independent reviewers and disagreement was resolved by a third reviewer. A total of 26 randomized clinical trials were identified through literature search (Figure 1 and Appendix 2). Out of these 26 studies, 16 had a cell therapy arm of 30 patients or more. Eventually, these 16 studies (5-7, 9-21) all agreed to participate in this collaborative overview and meta-analysis.

They provided the requested data, and vouched for the correctness of the data.

Endpoints, subgroups and data assembly

The following 3 endpoints were investigated in the analysis: change in LVEF (in %), LVESVI (in mL/m²), and LVEDVI (in mL/m²) from baseline to follow-up. The preferred follow-up duration was 6 months. If not available, outcome at 3 or 4 months was used.

The following subgroups were defined by the baseline characteristics : 1) age <55 years/ ≥55 years, 2) diabetes mellitus yes/no, 3) symptom to PCI time < 6 hours/ ≥6 hours, 4) infarct related artery left anterior descending artery / right coronary artery or left circumflex artery, 5) baseline LVEDVI <100 mL/m²/ ≥100 mL/m², 6) baseline LVEF <40% / ≥40%, 7) infarct size <20 g/≥20 g on Magnetic Resonance Imaging (MRI), and 8) microvascular obstruction presence/absence on MRI. Furthermore, we requested data on 9) time from primary PCI to cell infusion <7 days/ ≥7 days and 10) total number of injected mononuclear BMC $<10^8$ / $\geq 10^8$. The subgroups cut-off points were chosen based on the results of the previous cell therapy studies. Lastly we compared 2 trial characteristics, namely type of imaging modality (MRI versus other) and study design (double blinded randomized controlled trials compared to open label studies).

The principal investigator of each identified trial provided summary data (number of patients and mean ± standard deviation (SD)) of the 3 different endpoints and 10 different prespecified subgroups.
For the current analysis, subgroups and baseline timing of the measurement of LV function were defined as reported in each of the individual trials. When several methods were used for outcome assessment, MRI data were preferentially included in the analysis, followed by single photon emission computed tomography, echocardiography and LV angiography.

Statistical analysis

An overall meta-analysis was performed of the change in the 3 outcomes (LVEF, LVESVI and LVEDVI), based on random-effects models using the method described by DerSimonian and Laird (22). Results are presented as absolute changes from baseline to follow-up, with their 95% confidence intervals (CIs), per subgroup. Differences in treatment effects between subgroups were tested with heterogeneity test from Review Manager version 5.0. This test is based on the notion of performing a test for heterogeneity across subgroups rather than across studies. It measures the extent of inconsistency across the subgroups' results, and is interpreted as approximately the proportion of total variation in subgroup estimates that is due to genuine variation across subgroups rather than sampling error. For the subgroup based on infarct size on MRI, the analysis was restricted to those 6 trials that had these data.(7, 11, 13, 15, 16, 21, 23) The presence or absence of microvascular obstruction on MRI was available only in 7 trials.(6, 7, 11, 15-17, 19, 21) For the analysis regarding time from primary PCI to cell infusion <7 days/ ≥7 days and total number of injected mononuclear BMC $<10^8$ / $\geq 10^8$, the specific BMC therapy group was compared to controls in which sham infusion was performed. In trials where no sham infusion was performed, the comparator was compared to the entire control group. In the analysis of total number of injected mononuclear BMC $<10^8$ / $\geq 10^8$, we excluded 3 studies which used nucleated BMC or selected $CD34^+$/ $CXCR4^+$ cells. (5, 20, 21) Subgroup analyses were not adjusted for multiple testing.

Results

The participating trials randomized 1641 patients to intracoronary cell therapy (n=984) or standard therapy (n=657). Characteristics of the studies included in this review are listed in Table 1. Mean age across studies ranged from 50 – 61 years. Six studies included only patients with an anterior myocardial infarction. All STEMI patients were treated with primary PCI, except in the FINCELL study where patients were treated with thrombolysis first and later with PCI and cell infusion (12). Six

studies performed BMC aspiration in the control group and 7 studies performed sham infusion. Three trials did not infuse mononuclear BMCs but selected $CD34^+$/ $CXCR4^+$ cells or nucleated BMC, respectively (5, 20, 21). Methodological quality assessment of included studies is available in Appendix 3. Trials fulfilled our markers of validity.

In this analysis, 1494 patients had complete baseline and follow-up LVEF measurement, 1427 patients complete LVEDVI measurements (5 patients were missing from one trial (5) and LVEDVI was not available in another trial n=62 (20)) and 1349 patients complete LVESVI measurements (5 patients missing from one trial (5) and LVESVI data was not available in 2 trials, n=62 and n=78 (12, 20)).

Patient Characteristics

The absolute incremental improvement in LVEF was greater among BMC treated patients compared to controls: 2.55% increase (95% CI 1.83 to 3.26, p<0.001), Figure 2. Assessment of publication bias using visual examination of the funnel plot of the primary publications indicated no significant publication bias (Appendix 4). There was heterogeneity across study outcomes (I2=70%)

Treatment benefit in terms of LVEF improvement was more pronounced in patients with baseline LVEF <40% (5.30%, 95% CI 4.27 to 6.33) compared to LVEF ≥40% (1.45%, 95% CI 0.60 to 2.31, p<0.001). Also, patients < 55 years of age had more benefit from BMC therapy (3.38%, 95% CI 2.36 to 4.39) compared to patients age ≥55 years (1.77%, 95% CI 0.80 to 2.74, p=0.03). No significant interaction was observed between other subgroups and LVEF.

The overall effect of change of LVEDVI was -3.17 mL/m² in favour of BMC treatment (95% CI -4.86 to -1.47, p=0.<0.001, Figure 3). This decrease was more pronounced in patient with age <55 years (-5.70 mL/m², 95% CI -9.18 to -2.21), compared to patients ≥55 years of age (-1.13 mL/m², 95% CI

-4.58 to 2.32, p=0.001).

There was a significant decrease in change of LVESVI in the BMC group compared to the control group with a treatment effect of -2.60 mL/m^2 (95% CI -3.84 to -1.35, p<0.001, Figure 4). Again, patients with age<55 years benefit most from BMC compared to age ≥55 years (-4.47 ml/m², 95% CI -7.32 to -1.62 versus -0.82 ml/m², 95 % CI -3.31 to 1.67, p=0.002). Also, patients with baseline LVEF <40% had a more pronounced decrease in LVESVI (-4.74 mL/m², 95% CI -10.23 to 0.74) compared to LVEF ≥40% (-0.91 mL/m², 95% CI -2.48 to 0.66), p <0.001). There was also an interaction between baseline LVEDVI and treatment effect. Patients with a smaller EDV at baseline had less treatment effect.

Trial Characteristics

There was no difference in LVEF improvement between patients treated with cell infusion <7 days from primary PCI compared to ≥7 days (1.46%, 95% CI 0.41 to 2.51 versus 2.69%, 95% CI 1.80 to 3.58, p=0.08). Furthermore, we found no difference in LVEF improvement comparing patients with number of injected mononuclear BMC of <10^8 compared to ≥ 10^8 (2.80%, 95% CI 0.79 to 4.80 versus 0.58%, 95% CI -0.44 to 1.59, p=0.05), Table 2. Studies, using MRI as LV function assessment had a smaller treatment effect in LVEF when compared to non MRI studies (0.16% 95% CI -0.88 to 1.20 versus 4.67%, 95% CI 3.69 to 5.66, p<0.001). There was no clear interaction between study design, (blinded 1.36% 95% CI -0.04 to 2.76 versus open label 2.97%, 95% CI 2.14 to 3.80, p=0.05). These results were largely consistent in LVEDVI and LVESVI (Table 2).

Discussion

In this collaborative meta-analysis, we found that autologous BMC infusion is associated with a moderate but statistically significant improvement of LV systolic function and remodeling in

patients after ST-segment elevation myocardial infarction . This is reflected by a larger increase in LVEF and a greater decrease in LVESVI and LVEDVI in the treated population. In additional subgroup analyses, younger patients and patients with more depressed LVEF at baseline had the largest benefit from BMC infusion.

Previous meta-analyses have reported similar or somewhat larger benefit from BMC infusion then we observed. These meta-analyses reported, incremental LVEF changes of 2.7%(24) and 3.0% (2), to 4.0% (25) in the most recent meta-analysis. However, the last and most recent meta-analysis included all patients with ischemic heart disease, irrespective of study design (cohort study or randomized trials)(25). Also, this meta-analysis conducted by Jeevanantham et al. did not include 3 large randomized controlled trials (BONAMI, HEBE, and REGENT trial) that were included in our analysis. Moreover, we have included only trials with at least 30 patients in the treatment arm.

In our analysis, younger patients benefit more from cell therapy in terms of LV remodelling. Aging is a significant predictor of impairment of endothelium-dependent vasodilation and there is an increased risk of atherosclerotic disease and poor outcomes in older patients. The accumulation of risk factors in the older population is linked to a decrease in both the absolute number as well as the function of stem cells.(26)

However, aging itself seems to have a very strong influence on stem cell function and is accompanied by a decline in the homeostatic and regenerative capacity of all tissues and organs.(27) Both experimental as well as clinical studies have shown lower absolute numbers as well as functionality of stem cells with increasing age (8, 28). BMCs isolated from younger-aged rats showed increased efficacy in restoring LV function after myocardial infarction as compared to BMCs isolated from middle-aged rats.(28)

In patients with chronic ischemic heart disease, a similar relation between age and stem cell function has been shown.(29, 30) In the conducted BMC therapy clinical trials, autologous BMCs are typically

harvested from older patients who have recently suffered a myocardial infarction. In contrast, experimental studies in rodent models typically utilize donor BMCs isolated from young, healthy, inbred mice that are not the recipients. It has been postulated that this explains the much greater benefit of BMC therapy as observed in experimental studies.(31)
This might also have important implications for the therapeutic application of cell therapy. Future research should therefore focus on elucidating the crucial differences between young and aged BMCs and to reverse or alter these characteristics before delivery in a clinical setting.

In addition to younger age, we observed that patients with a more severely depressed LVEF at baseline had larger benefit from cell therapy. In fact, the effect in patients with an EF over 40% was practically non-existent whereas in the group of patients with an EF<40% the increase was substantial showing an improvement of 5%. It is conceivable that such an improvement could alter the clinical outcome in this high-risk population. Again, this has implications for the design of future clinical trials. Especially at the present time, when most studies are designed as proof-of-principle studies instead of large clinical-outcome studies, the selection of patients is of utmost importance and should contain subjects with the largest potential benefit of the intervention.

Although reduced LVEF is associated with the presence of microvascular obstruction and larger MRI infarct sizes, we did not find an association between the presence of microvascular obstruction or infarct size and the effects of BMC infusion. However, these MRI parameters were only present in less than 37% of the patients included in this analysis and therefore results should be interpreted with caution.

Diabetes mellitus is one of the key risk factors for coronary artery disease, and its prevalence is expected to increase in the coming years. Diabetes mellitus leads to dysfunction of the endothelium

and the microcirculation. Theoretically this could lead to a diminished response to BMC infusion, hampering adhesion and homing of these cells to the area of interest. Also the functionality and the absolute number of stem cells are reduced in diabetes mellitus. (32, 33) The reduction in cells was directly related to levels of HbA1c.(33) Another study showed that the reduced number of $CD34^{+}KDR^{+}$ cells was associated with the severity of diabetic vasculopathy.(34) Nevertheless, we did not observe a relationship between presence of diabetes mellitus and efficacy of BMC infusion in our analysis. It should be noted though that our study population consisted of less than 16% of patients with diabetics.

Although the effect of BMC infusion on LVEF seems to be small it should be noted that other treatment modalities like beta-blocker therapy or direct revascularization also have a relatively small influence on LVEF improvement.(35) The question remains what the long term effects of a single intracoronary BMC infusion are on LV function and remodeling and clinical outcomes. Additional meta-analyses are performed to address this question (24, 36) but studies with long term follow-up still remain limited. The large BAMI trial, funded by the European Union, will investigate BMC therapy in a RCT with primary clinical endpoints in a STEMI population with 3000 patients and a LVEF <45% (NCT01569178). Lastly, several different strategies of cell isolation and infusion have been applied and it yet remains to be determined which is the most effective regimen.

Limitations

There are some limitations to our analysis that should be taken into account. As with any meta-analysis, limitations to the method include heterogeneity across trials. In particular, there are differences in terms of treatment characteristics including used cell dosage, cell isolation protocols, storage methods, and image modalities. Morover, in our analysis, we have excluded trials with a cell therapy arm <30 participants (number of excluded patients is 322 (16%)). We excluded the smaller

trials for several reasons. First, we believe that subgroup assessment in these trials are less valuable due to small numbers. Second, we feel that publication bias is a larger problem in these small trials. Third, to our opinion, cell therapy involves a comprehensive protocol that involves a learning curve.

Conclusion

This is, to our knowledge, the first collaborative meta-analysis to assess the effects of intracoronary BMC therapy. Intracoronary BMC therapy leads to a modest but significant improvement of LV function in patients after STEMI. Patients of younger age and with a more severely depressed LVEF showed the largest benefit. This should be taken into account when designing future trials using intracoronary BMC infusion as an adjunctive therapy for STEMI. Most importantly, trials like the ongoing BAMI-trial that are powered to determine the effects of BMC infusion on clinical endpoints need to be awaited. Such trials will show whether the modest improvement of LV function translates in true clinical benefit.

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Competing interests, financial disclosure and an ethics statement

No authors have any competing interests, an ethics statement was not required for this work and no funding was received for this work.

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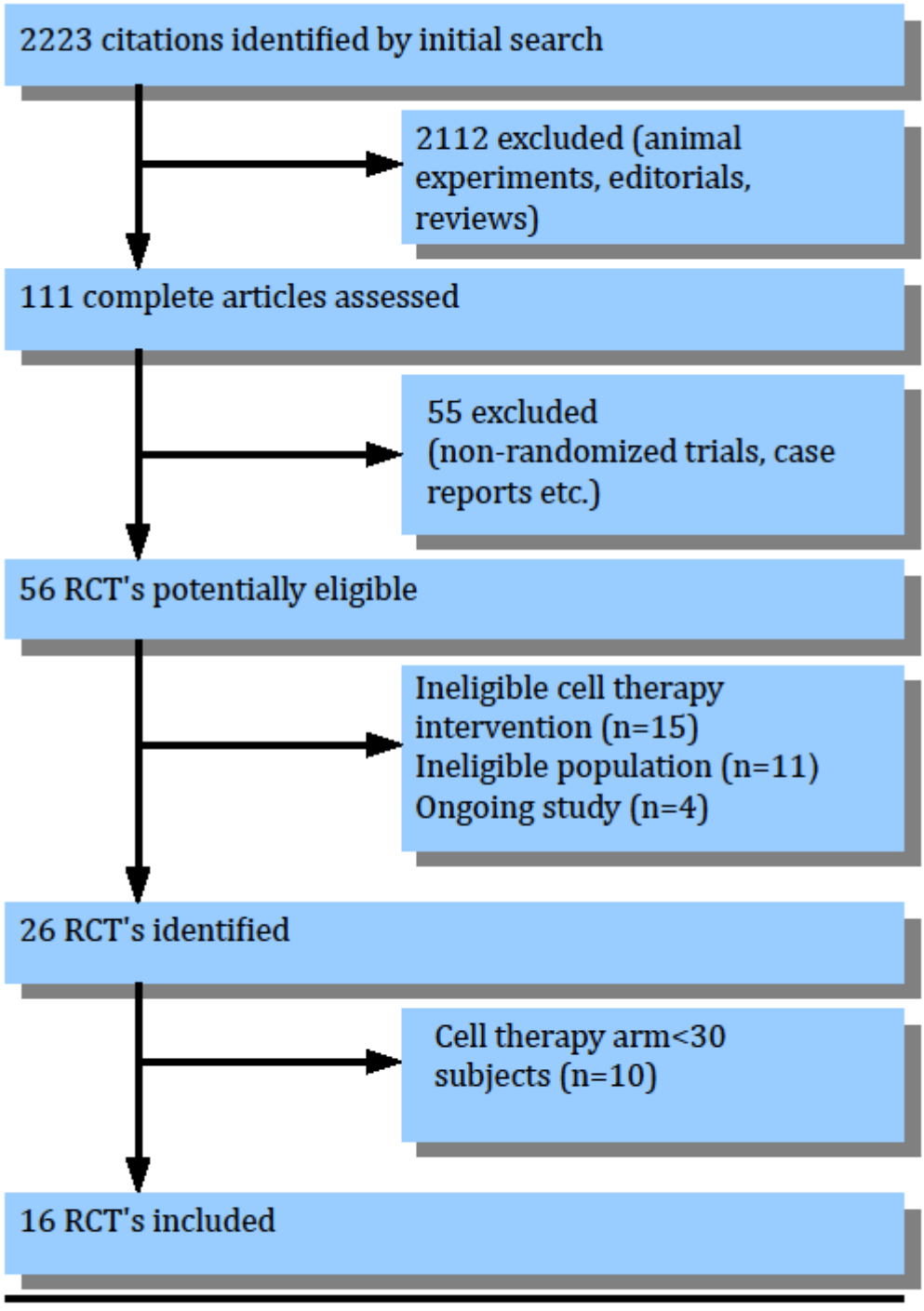
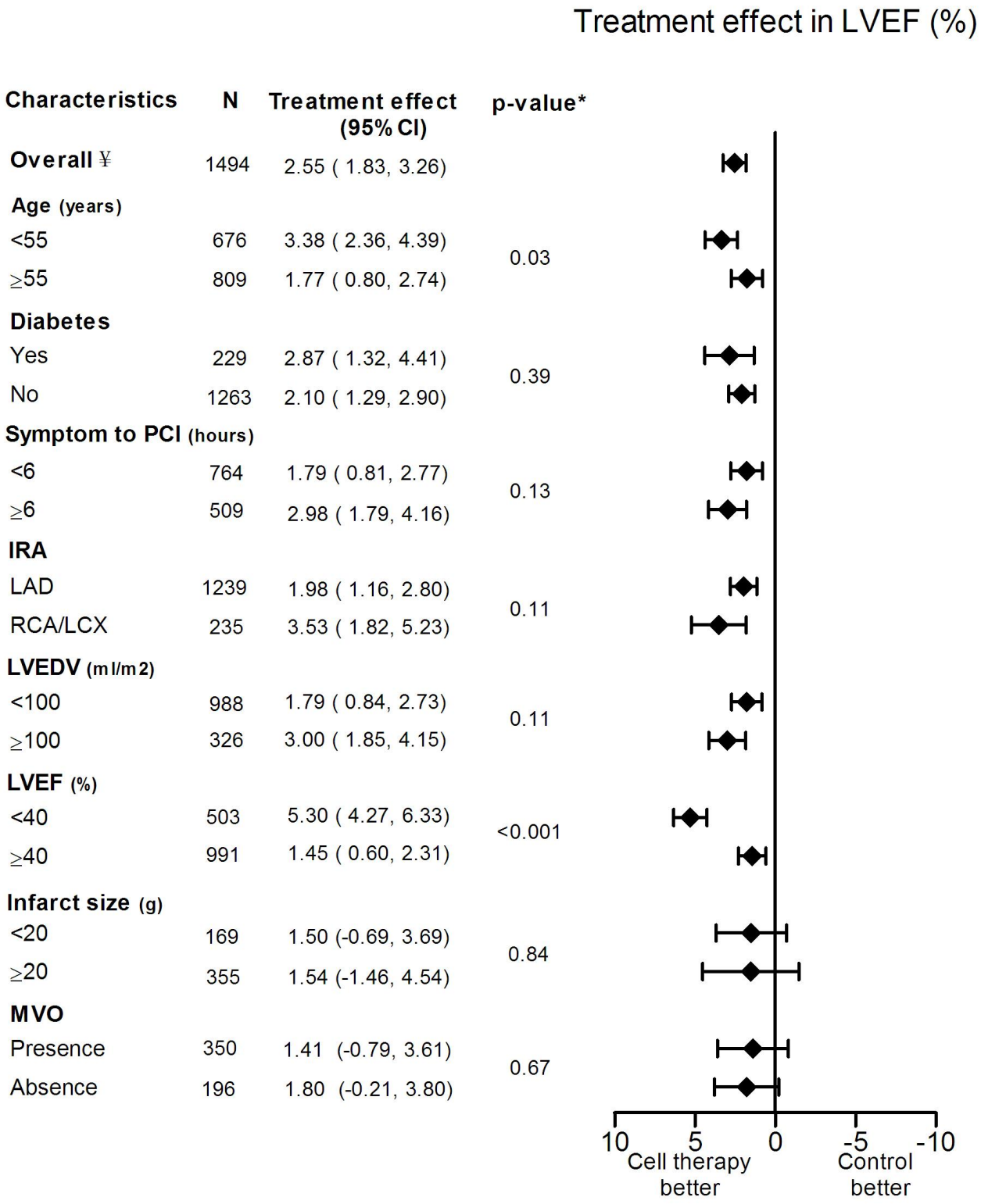
Figure 1. Flow diagram of studies included in this meta-analysis



RCTs, randomized controlled trials
See Appendix 2 for a list of identified studies

Figure 2. Pooled improvement of left ventricular ejection fraction (LVEF) of included cell therapy trials assessing different subgroups

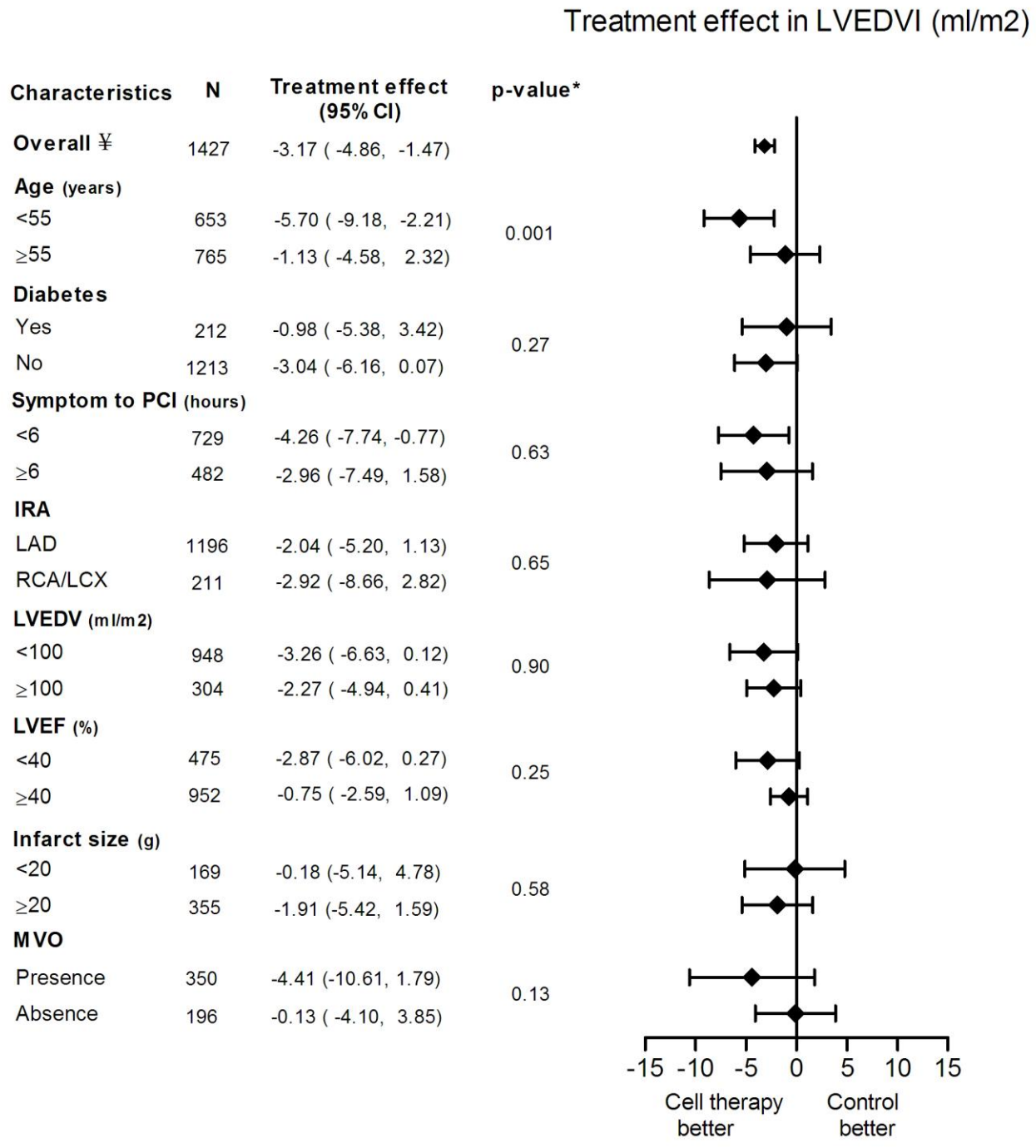


CI, confidence interval; IRA, infarct related artery; LAD, left anterior descending artery; LCX, left circumflex artery; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; MVO, microvascular obstruction; PCI, percutaneous coronary intervention; RCA, right coronary artery.

¥ frequencies can vary across subgroups due to missing baseline characteristics values

* p-value for subgroup differences

Figure 3. Pooled improvement of left ventricular end-diastolic volume index (LVEDVI) of included cell therapy trials assessing different subgroups

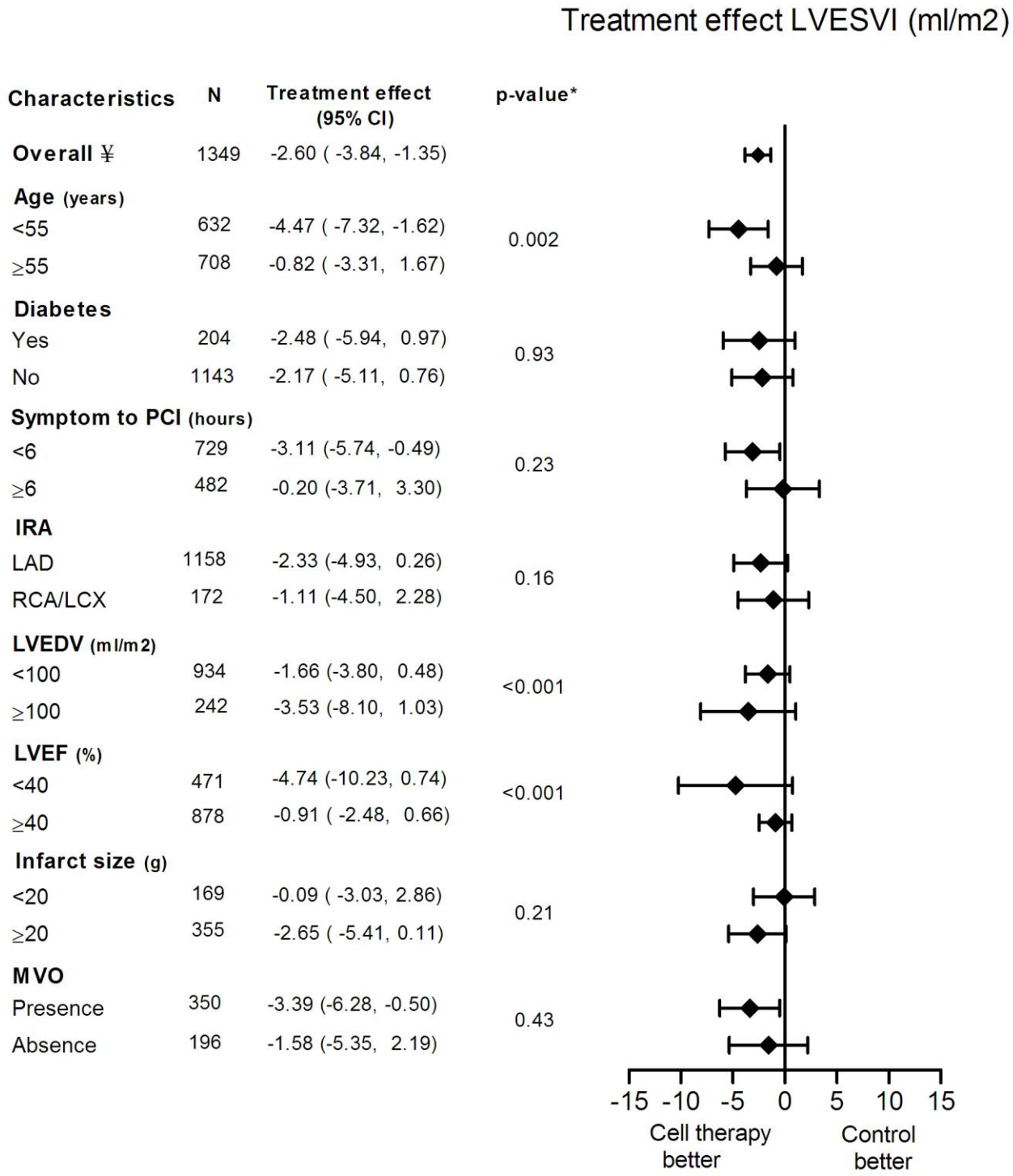


CI, confidence interval; IRA, infarct related artery; LAD, left anterior descending artery; LCX, left circumflex artery; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; MVO, microvascular obstruction; PCI, percutaneous coronary intervention; RCA, right coronary artery.

¥ frequencies can vary across subgroups due to missing baseline characteristics values

* p-value for subgroup differences

Figure 4. Pooled improvement of left ventricular end-systolic volume (LVESVI) of included cell therapy trials assessing different subgroups



CI, confidence interval; IRA, infarct related artery; LAD, left anterior descending artery; LCX, left circumflex artery; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; MVO, microvascular obstruction; PCI, percutaneous coronary intervention; RCA, right coronary artery.

¥ frequencies can vary across subgroups due to missing baseline characteristics values

* p-value for subgroup differences

Table 1. Characteristics of individual studies included in this review

Author (year)	N	BMC versus control	Mean Age (years)	Mean Baseline LVEF (%)	Days from onset STEMI to BMC infusion	BMC aspiration/ Sham infusion in control arm	Cell type	Number of injected cells ($x10^8$)	Volume bone marrow aspiration (mL)	Imaging modality for endpoint assessment	Days from STEMI to baseline LVEF assessment	Core lab assessment of imaging endpoint	Follow-up (months)
Cao et al. (2009)	86	1:1	51	Tx) 41 ± 3 C) 41 ± 3	7	No / Yes	MN BMC	0.5 ± 0.1	~40	2D-TTE	7	No	6
Grajek et al. (2010)	45	2:1	50	Tx) 45 ± 10 C) 43 ± 7	4 – 6	No / No	MN BMC	4.1 ± 1.8	80 ± 30	EF-RNV	4 – 6	No	6
Hirsch et al. (2010)	134	1:1	56	Tx) 44 ± 9 C) 42 ± 8	3 – 7	No / No	MN BMC	3.0 ± 1.6	~60	MRI	3 (2 – 4)	Yes	4
Huikuri et al. (2008)	80	1:1	59	Tx) 59 ± 11 C) 62 ± 12	3 ± 2	Yes / Yes	MN BMC	4.0 ± 2.0	~80	LV Angio (biplane)	during PCI	Yes	6
Janssens et al. (2006)	67	1:1	57	Tx) 49 ± 7 C) 47 ± 8	Within 1 day	Yes / Yes	MN BMC	3.0 ± 1.3	130 ± 22	MRI	4 (3 – 5)	No	4
Lunde et al. (2006)	100	1:1	57	Tx) 55 ± 14 C) 54 ±12	4 – 8	No / No	MN BMC	0.7 (0.5 – 1.3)	~50	MRI	19 ± 4	No	6
Plewka et al. (2009)	60	2:1	56	Tx) 35 ± 6 C) 33 ± 7	7 ± 2	No / No	MN BMC	1.4 ± 0.5	~100	2D-TTE	3	No	6
Roncalli et al.(2010)	101	1:1	56	Tx) 37 ± 10 C) 39 ± 9	9 ± 1	No / No	MN BMC	1.0 ± 0.09	~50	MRI	7 ± 2	Yes	3
Schachinger et al. (2006)	204	1:1	56	Tx) 48 ± 9 C) 47 ± 10	4 ± 1	Yes / Yes	MN BMC	2.4 ± 1.7	~50	LV angio (biplane)	4 ± 1	Yes	4
Sürder et al (2013)	200	2:1	58	Tx) 36 ± 10 C) 40 ± 10	5 – 7 21 – 28	No / No	MN BMC	1.5 ± 1.2	68 ± 15	MRI	6 (4 –8)	Yes	4
Tendera et al. (2009)	200	2:1	57	Tx) 40 ± 10 C) 40 ± 9	3 – 12	No / No	MN BMC Selected $CD34^+$/ $CXCR4^+$ cells	1.8 0.02	50 – 70 100 – 120	MRI	4 – 15	No	6
Traverse et al. (2010)	40	3:1	54	Tx) 49 ± 10 C) 49 ± 9	5 ± 2	Yes / Yes	MN BMC	1.0	50 – 70	MRI	3 ± 2	No	6
Traverse et al. (2011)	87	2:1	57	Tx) 49 ± 12 C) 45 ± 10	17 (16 – 20)	Yes / Yes	MN BMC	1.5 ± 0.2	80 – 90	MRI	17	Yes	6
Traverse et al. (2012)	120	2:1	57	Tx) 45 ± 11 C) 45 ± 11	3 (3 – 4) 8 (7 – 8)	Yes / Yes	MN BMC	1.5 ± 0.2	80 – 90	MRI	3	Yes	6
Turan et al. (2012)	62	2:1	61	Tx) 43 ± 10 C) 45 ± 10	7	No / No	Nucleated BMC	96 ± 32	~120	LV Angio (biplane)	7	No	3
Wollert et al. (2004)	60	1:1	56	Tx) 50 ± 10 C) 51 ± 9	6 ± 1	No / No	Nucleated BMC	25 ± 9	128 ± 33	MRI	4 ± 2	No	6

BMC, bone marrow cells; EF-RNV, ejection fraction radionuclide ventriculography; LVEF, left ventricular ejection fraction; LV, left ventricle; LV angio, left ventricular angiography; MN BMC, mononuclear bone marrow cells; MRI, magnetic resonance imaging; N, number of patients; PCI, percutaneous coronary intervention; STEMI; ST-segment Elevation Myocardial Infarction; TTE, Transthoracic Echocardiogram
Tx) treatment arm, C) control arm

Table 2. Treatment effect of different trial characteristics included in this meta-analysis

	LV ejection fraction (%)			LV end-diastolic volume index (ml/m^2)			LV end-systolic volume index (ml/m^2)		
	N	Treatment effect (95% CI)	p-value*	N	Treatment effect (95% CI)	p-value*	N	Treatment effect (95% CI)	p-value*
Time from PCI to cell infusion									
< 7 days	836	1.46 (0.41 to 2.51)	0.08	802	-3.53 (-5.89 to -1.18)	0.62	802	-2.88 (-4.70 to -1.06)	0.41
≥7 days	769	2.69 (1.80 to 3.58)		640	-4.36 (-6.66 to -2.05)		640	-3.94 (-5.69 to -2.19)	
Total number of injected BMC									
<1x 10^8	314	2.80 (0.79 to 4.80)	0.05	314	-4.72 (-8.15 to -1.29)	0.34	314	-6.36 (-9.46 to -3.27)	0.01
≥1x 10^8	1005	0.58 (-0.44 to 1.59)		1005	-2.78 (-4.85 to -0.70)		927	-1.97 (-3.58 to -0.36)	
Imaging modality for LV function									
MRI	981	0.16 (-0.88 to 1.20)	<0.001	976	-1.50 (-3.82 to 0.82)	0.02	976	0.16 (-1.54 to 1.85)	<0.001
Other	513	4.67 (3.69 to 5.66)		451	-5.63 (-8.11 to -3.15)		373	-5.85 (-7.69 to -4.01)	
Study design									
Blinded	558	1.36 (-0.04 to 2.76)	0.05	558	-1.93 (-4.96 to 1.09)	0.24	480	-2.41 (-4.60 to -0.21)	0.84
Open label	936	2.97 (2.14 to 3.80)		869	-4.11 (-6.16 to -2.06)		869	-2.69 (-4.20 to -1.17)	

BMC, bone marrow cells; CI, confidence interval; LV, left ventricular; MRI, magnetic resonance imaging; N, number of patients; PCI, percutaneous coronary intervention
** p-value for subgroup differences*